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Cardiovascular-related Mortality in Generally Healthy Adults with High Levels of Parathyroid Hormone

Abstract

Background: Cardiovascular-related deaths account for nearly 30% of deaths worldwide. Age, diabetes mellitus, the male gender, and use of tobacco products have been identified as risk factors in previous studies; however, most recent research is directing attention toward other causes of cardiovascular-related mortality. Parathyroid hormone (PTH), an important component in the maintenance of mineral homeostasis, has shown to be linked to cardiovascular events when the levels are high. As a result, it becomes fundamental to seek the relationship between elevated levels of PTH in a generally healthy population aged 50 and older and cardiovascular-related mortality.

Methods: An exhaustive literature search was conducted using the following search engines: Medline-OVID, Web of Science, and CINAHL. For each literature search, the key words *parathyroid hormone*, *cardiovascular*, *mortality*, and *adult* were utilized to narrow the results. The following inclusion criteria were required in narrowing the search: studies including adults aged 50 and older, studies that measure cardiovascular-related mortality as the primary outcome, studies that investigate elevated PTH in generally healthy populations, and studies with a mean follow-up of at least seven years. Similarly, the following exclusion criteria were applied to the search: studies published before the year 2009, studies not performed on humans, and studies in a language other than English. All articles were assessed for quality using GRADE.

Results: The search resulted in 156 articles, all of which were viewed for relevancy. After the application of inclusion and exclusion criteria, two community-based cohort studies were included. Both observational studies demonstrated a positive correlation between increased parathyroid hormone and cardiovascular mortality in community-dwelling adults over the age of 50. The primary outcome measured was cardiovascular mortality, and no other surrogate outcomes were used. After the GRADE assessment, both prospective cohort studies were considered to be low quality.

Conclusion: Two observational studies show a correlation between high parathyroid hormone and cardiovascular-related mortality in populations of generally healthy community-dwelling adults. At this time, the low quality evidence is not enough to support the correlation. However, due to these findings, future studies may possibly confirm use parathyroid hormone as a modifiable risk factor in the prevention of cardiovascular-related mortality.

Keywords: Parathyroid hormone, cardiovascular, mortality, and adult

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First Advisor

James Ferguson, PA-C

Second Advisor

Annjanette Sommers, MS, PA-C

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Cardiovascular-related Mortality in Generally Healthy Adults with High Levels of Parathyroid Hormone

Robyn Nash



A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 8th 2015

Faculty Advisor: James Ferguson, PA-C

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS

Biography

Robyn Nash has spent the entirety of her life in Southern California, where she majored in Health Science at California State University, Fullerton. While finishing up her undergraduate degree in the Spring of 2012, she obtained her EMT certificate and began working as an Emergency Room Technician at the same hospital at which she had volunteered for the previous three years. She plans to begin working in Family Practice, but has great interest in Orthopedics and Dermatology.

Abstract

Background: Cardiovascular-related deaths account for nearly 30% of deaths worldwide. Age, diabetes mellitus, the male gender, and use of tobacco products have been identified as risk factors in previous studies; however, most recent research is directing attention toward other causes of cardiovascular-related mortality. Parathyroid hormone (PTH), an important component in the maintenance of mineral homeostasis, has shown to be linked to cardiovascular events when the levels are high. As a result, it becomes fundamental to seek the relationship between elevated levels of PTH in a generally healthy population aged 50 and older and cardiovascular-related mortality.

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List of Abbreviations

BMI.....	Body Mass Index
CKD.....	Chronic Kidney Disease
CVD.....	Cardiovascular Disease
GFR.....	Glomerular Filtration Rate
GRADE.....	Grading of Recommendations, Assessment, Development and Evaluations
HDL.....	High Density Lipoprotein
HR.....	Hazard Ratio
ICD.....	International Classification of Diseases
RAAS.....	Renin-Angiotensin-Aldosterone System
PTH.....	Parathyroid Hormone
SBP.....	Systolic Blood Pressure
SD.....	Standard Deviation

Cardiovascular-related Mortality in Generally Healthy Adults with High Levels of Parathyroid Hormone

BACKGROUND

Approximately 30% of deaths worldwide and nearly 40% of deaths in high-income countries can be attributed to cardiovascular-related causes.¹ Factors including the male gender, reduced HDL cholesterol levels, use of tobacco products, age, and diabetes mellitus have been shown to increase risk of cardiovascular-related mortality; however, further research has begun to point toward other potential causes.² Parathyroid hormone (PTH), a key regulator in the homeostasis of magnesium, calcium and phosphate levels, has the ability to result in cardiovascular-related events when elevated or diminished levels are present.³ Since approximately 9-15% of females and a slightly lower level of males in the United States adult population have some type of thyroid disease, this phenomenon becomes of vital importance to investigate.^{3,4}

There have been several studies that have conveyed a positive correlation between high levels of PTH and cardiovascular-related mortality in Chronic Kidney Disease (CKD) patients, which have resulted due to a mineral imbalance.⁴ Similarly, another study noted that PTH levels above 65 pg/mL in healthy members of a population increases their risk for heart failure by 30% (95% CI: 6% to 61%).⁵ With history of this evidence, placing emphasis on research in generally healthy community-based populations will help establish a new framework behind the function of PTH and encompass an expanded group of individuals. Although the effects of high PTH have

been researched regarding cardiovascular events, the rate of cardiovascular-related mortality should be further explored.

Additionally, another prospective cohort study⁶ revealed that PTH receptors are located body wide, which indicates the potential of PTH to affect the nervous, skeletal, cardiac, and renal systems, potentially leading to cardiovascular disease (CVD) risk and mortality. By inspecting the mechanism of action regarding high PTH, further research can be performed to develop an understanding of the systematic effects on the body. Specifically, activation of the renin-angiotensin-aldosterone system (RAAS) results in cardiac remodeling and high blood pressure. Elevated PTH induces hardening of the arteries and vascular inflammation.⁶ By increasing levels of calcium within the cells, a natural response of elevated PTH, left ventricular hypertrophy and calcification of the heart valves can occur.⁵ Overall, these mechanisms serve as a basis in understanding the role in cardiovascular-related mortality.

By identifying risk factors, such as elevated PTH, in patients within clinic, it becomes more reasonable and measureable to monitor and prevent complications. With the potential of elevated PTH having public health implications, identifying it as a risk factor is of vital importance in early detection of cardiovascular risks. For the reasons mentioned above, it becomes fundamental to seek the relationship between elevated levels of PTH in a generally healthy population aged 50 and older and cardiovascular-related mortality.

METHODS

An exhaustive literature search was conducted using the following search engines: Medline-OVID, Web of Science, and CINAHL. For each literature search, the key words *parathyroid hormone*, *cardiovascular*, *mortality*, and *adult* were utilized to narrow the results. The following inclusion criteria were required in narrowing the search: (1) studies including

adults aged 50 and older, (2) studies that measure cardiovascular-related mortality as the primary outcome, (3) studies that investigate elevated PTH in generally healthy populations, and (4) studies with a mean follow-up of at least seven years. Similarly, the following exclusion criteria were applied to the search: (1) studies published before the year 2009, (2) studies not performed on humans, and (3) studies in a language other than English. After application of inclusion and exclusion criteria to determine applicability, the GRADE system served to assess the quality of each remaining study.⁷

RESULTS

The search resulted in 22 articles via Medline-OVID, 119 via Web of Science, and 15 via CINAHL, for a total of 156 articles. These articles were all reviewed and screened for relevancy by use of the inclusion and exclusion criteria, which resulted in the utilization of two cohort studies.^{6,8}

Ballegooijen et al

This prospective cohort study⁶ sought to investigate elevated PTH levels and its association with cardiovascular-related mortality in a general population. A total of 633 participants were included in the study, with an average age of 70.1 ± 6.6 years. Initially, the first group of individuals invited to participate in the study were those with impaired glucose levels (n=193), diabetes type 2 (n=176), and normal glucose levels (n=705). Only 648 of these individuals decided to participate. An additional 188 people with type 2 diabetes were invited to participate. However, those without serum PTH values were excluded from the study. Ingestion of lithium medication was also considered exclusion criteria, since calcium levels may be altered. The specific selection methodology was not mentioned. Overall, the primary outcomes of the study were cardiovascular mortality and all-cause mortality, which were categorized by

the use of International Classification of Diseases (ICD) codes 390 to 459 (circulatory system diseases) or 798 (sudden death).⁶

After the application of eligibility criteria, baseline measurements, demographics, lifestyle habits, dietary variables, metabolic variables, and cardiac measures were recorded for each participating individual and utilized to maintain prognostic balance throughout the study. These groups demonstrated prognostic balance. PTH quartiles were also created to seasonally classify the results, with the lower three quartiles serving as a reference group. Since vitamin D levels fluctuate depending on the level of sun exposure, classifying the information into seasonal groups will eliminate a potential confounding variable. Statistical results were also adjusted for age, gender, level of education, systolic blood pressure (SBP), use of tobacco products, BMI, GFR, microalbuminuria, and use of antihypertensive medications. By using Kaplan-Meier analysis, the differences in survival between the four PTH quartiles were represented graphically.⁶

After a median follow-up of 7.8 years, 18% of participants died (n=112), and 23% of the deaths (n=26) were determined to be cardiovascular-related. The Kaplan-Meier curve illustrated a significantly decreased survival in quartile 4, which had the highest PTH levels (P=0.022). By using a threshold model where the three lowest quartiles are used as a reference group (quartile 4 versus quartile 1-3), there was a significant association between cardiovascular-related mortality and high PTH; HR =2.56 (1.11, 5.94; P=0.028).⁶

Hagstrom et al

This prospective cohort study⁸ sought to investigate the risk of cardiovascular mortality in relation to high PTH in the community. Initially, 1221 individuals were invited to complete a health survey, which identified cardiovascular-related risk factors. Of these participants, a total

of 958 were included in the study because their PTH measurements were valid. However, the specific methodology for selecting these individuals is not mentioned. The average age of the participants was 71. To further rule out confounding variables, the final group was analyzed in several subgroups: (1) those without previous CVD (n=617), (2) those with a PTH level in the normal range (<6.8 pmol/L; n=868), and (3) those with normal levels of calcium (2.2 to 2.6 mmol/L), GFR ($>50 \text{ mL} \times \text{min}^{-1} \times 1.73 \text{ m}^{-2}$), and vitamin D levels ($>37.5 \text{ nmol/L}$; n=646). Overall, the primary outcomes of the study were cardiovascular mortality and all-cause mortality, which were categorized by the use of ICD-9 codes 390 to 459 or ICD-10 codes 100-199.⁸

After all participants gave written consent, baseline measurements, demographics, lifestyle habits, dietary variables, metabolic variables, and cardiac measures were recorded for each participating individual and utilized to maintain prognostic balance throughout the study. There was prognostic balance with these demographics. Specifically, statistical results were adjusted for age, SBP, BMI, use of tobacco products, diabetes mellitus, HDL cholesterol, use of antihypertensive or lipid-lowering medications, and history of CVD.⁸

After a median follow-up of 9.7 years (1.2 to 12.4), a total of 277 individuals died. Of those 277 participants, 117 can be attributed to cardiovascular-related causes. When considering the entire sample size, there was a 37% to 38% higher cardiovascular-related mortality risk for every 1-SD rise in PTH. After accounting for previous cardiovascular risk factors as mentioned above, cardiovascular-related mortality showed to be associated with high PTH (HR: 1.39, 95% CI, 1.18 to 1.60; $P<0.001$). Regarding the subgroups (those without previous CVD, those with normal PTH, and those with normal mineral metabolism), there remained an association between

high PTH and cardiovascular-related mortality. Overall, high PTH (>5.27 pmol/L) accounted for 20% (95% CI, 10 to 26) of the cardiovascular-related deaths.⁸

DISCUSSION

After careful review of the selected articles,^{6,8} the data revealed a positive relationship between increased PTH and its link to cardiovascular-related mortality in generally healthy populations with individuals aged 50 and older. As mentioned previously, PTH is a key regulatory hormone in the balance of calcium, phosphate, and vitamin D and in maintaining homeostasis.¹⁰ When performing research on this relationship, it becomes important to distinguish one variable from the next. Seemingly, the diagnostic utility and use of serum PTH as a prognostic marker for chronic disease is increasing through the use of measuring other circulating PTH molecular forms. These fragment-specific samples will aid in the understanding of mineral homeostasis.¹¹ Regarding future research, this approach may be a helpful link in unravelling the complex relationship of these minerals, further helping to establish the role of PTH and adjust for potential confounders. One prospective cohort study¹² has attempted to research the relationship of all key metabolites and minerals involved in PTH, although more research is needed.¹² Similarly, another prospective cohort study¹³ investigated the impact of fibroblast growth factor 23 and its impact on the incidence of cardiovascular mortality due to its role in mineral metabolism.¹³ Once these complex relationships begins to unravel, the potential for PTH to become a modifiable risk factor is more realistic for future clinical practice. The differentiation between various ethnic groups will also help determine the role of PTH.¹⁴

Despite the positive correlation between cardiovascular-related death and high PTH in the Ballegooijen et al study⁶, there are several limitations that restrict complete confirmation of that data. Since this study⁶ is a prospective cohort study, the reliability of the design limits trust

in the outcomes. Additionally, there was a relatively low number of cardiovascular-related deaths (n=26). Although the study also intended to exclude the use of medications that would affect mineral metabolism, there was missing information about the utilization of bisphosphonates. Similarly, there was missing information on calcium and phosphate levels, which would have been impacted by the use of bisphosphonates.⁶ Considering these faults, it becomes difficult to use this data with full trust in the methodology behind the study. Lastly, there was a single PTH measurement at the beginning of the study, and additional samples were not taken throughout the years. Essentially, this is putting reliance on that idea that one baseline value has the potential to define consequences which are to follow years later. Since there has been no solid statistical evidence behind this strategy, it becomes questionable for whether or not this is the most effective approach.⁶

Although the Hagstrom et al study⁸ also determined there was a positive correlation between elevated PTH and cardiovascular-related mortality (in fact there appears to be a dose-response gradient in that as PTH levels increase so do mortality rates), there are several limitations that should be considered. Due to the fact that this is a prospective cohort study, the quality of the study is already significantly diminished to low. Additionally, this study⁸ focused on elderly men instead of the entire population. This makes the resulting data less generalizable to the community as a whole. Lastly, there was a single PTH measurement at the beginning of the study with no other measurements taken throughout the expanse of the research. As mentioned previously, there is no statistical evidence behind this approach, and there exists uncertainty in the effectiveness of the methodology.

Overall, future research is needed to enhance the understanding between PTH and cardiovascular-related mortality. Specifically, research should focus on deciphering whether or

not PTH levels or other minerals such as calcium, phosphate, or vitamin D levels are the primary concerning factor. Furthermore, research evaluating whether or not PTH levels can be manipulated and how this alteration can benefit patients is of great interest. To determine the utility of PTH in a risk assessment for evaluating chronic disease would be of utmost usefulness in patient evaluation.

CONCLUSION

As a result of this systematic review, the two reviewed studies showed a correlation between high PTH and increased risk of cardiovascular-related mortality in generally healthy community-based populations. Although PTH can easily be considered its own entity, it intertwines complexly with other minerals in the body. Its role with calcium, phosphate, and vitamin D make it difficult to disentangle the relationship and study each component separately.⁹ As a result, distinguishing each individual component becomes complex and needs further refinement in future studies. The need for randomized control trials in future studies also becomes of utmost interest to gain quality evidence behind these theories. Overall, it seems that the role of the relationship between elevated PTH and cardiovascular-related mortality in the generally healthy population is crucial to identifying key modifiable risk factors. Through further investigation, using PTH serum levels as a predictor of cardiovascular risk has the potential to become an important part of the future of healthcare.

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Characteristics of Reviewed Studies

Table I. van Ballegooijen et al⁶ and Hagstrom et al⁸

Quality Assessment							
		<i>Downgrade Criteria</i>					
<i>Study</i>	<i>Design</i>	<i>Limitations</i>	<i>Indirectness</i>	<i>Imprecision</i>	<i>Inconsistency</i>	<i>Publication bias likely</i>	<i>Quality</i>
Parathyroid Hormone							Low
Van Ballegooijen et al	Cohort	Not serious	Not serious	Not serious	Not serious	No	Low
Hagstrom et al	Cohort	Not serious	Not serious	Not serious	Not serious	No	Low

Summary of Findings

Table II. van Ballegooijen et al⁶

	<i>Baseline</i>	<i>Cardiovascular Mortality (median follow-up of 7.8 years)</i>		<i>P-value for trend</i>
Group (n = 633)	Mean Serum PTH (min, max) in pmol/L	Events (n = 26)	HR, 95% CI (min, max)	
Quartile 1 (n = 156)	3.9 (1.7, 4.8)	4	Reference	0.121
Quartile 2 (n = 158)	5.2 (4.3, 6.0)	5	1.23 (0.32, 4.64)	
Quartile 3 (n = 160)	6.3 (5.4, 7.3)	4	0.82 (0.20, 3.30)	
Quartile 4 (n = 159)	9.4 (6.6, 33.8)	13	2.58 (0.79, 8.36)	

Table III. Hagstrom et al⁸

	<i>Baseline</i>	<i>Cardiovascular Mortality (median follow-up of 9.7 years)</i>		<i>P-value</i>
Group (n = 958)	Mean Serum PTH in pmol/L	Events (n = 117)	HR, 95% CI (min, max)	
Quartile 1	<2.96	Unknown	Reference	>0.05
Quartile 2	2.96-3.99	Unknown	0.78 (0.43, 1.43)	>0.05
Quartile 3	4.00-5.27	Unknown	0.99 (0.56, 1.72)	>0.05
Quartile 4	>5.27	23	1.83 (1.10, 3.04)	<0.05